Chapter 28. Prevention of Venous Thromboembolism: Brief Update Review

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Introduction

Deep venous thrombosis (DVT) refers to occlusion within the venous system, most commonly of the lower extremities, which can lead to pulmonary embolism (PE), or embolism to the pulmonary vasculature. Venous thromboembolism (VTE), comprising PE and DVT, is estimated to account for 5 to 10 percent of all deaths among hospitalized patients,[1,2] and also is associated with significant morbidities. In 2008, the United States Surgeon General issued a Call to Action to Prevent DVT and PE. The report brings to light the huge numbers of patients afflicted by DVT (350,000-600,000) and killed by PE (>100,000) every year in the United States.[3] Even though high quality evidence exists for safe and effective strategies to reduce the risk of VTE, studies continue to show that many hospitalized patients are not given risk-appropriate VTE prophylaxis. One recent study across 32 countries found that only 59 percent of at-risk surgical and 40 percent of at-risk medical patients received guideline-recommended VTE prophylaxis[4] and a United States registry study found that only 42 percent of patients diagnosed with DVT during a hospitalization had received prophylaxis.[5]

The Agency for Healthcare Research and Quality (AHRQ) has indicated that delivery of appropriate VTE prophylaxis is an essential patient safety practice and one that can prevent in-hospital death.[6] As of 2011, the National Quality Forum (NQF) has 10 VTE-related standards and endorsed outcomes measures.[7] Evidence-based best practice prophylaxis varies by primary service (e.g. medicine, surgery, trauma, orthopedics) and patient risk factors. Risk of VTE among hospitalized patients varies based on several risk factors including medical condition, type of surgery, trauma, cancer, age, immobility, hypercoagulable state, and previous history of VTE. Most hospitalized patients have one or more VTE risk factors, and well-developed guidelines are available that specify which types of patients should receive prophylaxis measures, and which specific measures are most appropriate.[1]

The original report, Making Health Care Safer, reviewed the effectiveness, safety, cost-effectiveness, and indications for VTE prophylaxis. This review concluded that whereas VTE prophylaxis shows clear benefits for a number of conditions and minimal concerns regarding adverse events, the practice remains underused. A small number of interventions aimed at improving use of prophylaxis were reviewed. The current review provides an update on the most effective VTE prophylaxis regimens as well as on interventions aimed at improving adherence to guidelines on the use of these preventive strategies. A MEDLINE search was conducted from 2001 to 2011 to identify studies that assessed the effectiveness and safety of VTE preventive measures as well as those aimed at improving their use.

What Are the Practices for Preventing Venous Thromboembolism?

Both pharmacologic and mechanical prophylactic interventions have been demonstrated to be effective in preventing many VTE events and have been evaluated for their appropriateness for certain types of patients (medical vs. surgical) with certain risk factors.[1,8] Pharmacologic prophylaxis includes low dose unfractionated heparin; low-molecular weight heparins, including

enoxaparin, dalteparin, and fondaparinux; warfarin; and aspirin, along with newer classes of anti-thrombotic agents. Mechanical prophylaxis includes anti-embolic stockings and intermittent pneumatic compression devices. Because the underlying approach of all prophylaxis medications is to decrease clotting, they may increase the risk of bleeding. The balance between bleeding and clotting must be considered in every patient, and the benefits and harms must be weighed before administering these drugs. For this reason, patient risk stratification is paramount to ensure that only at-risk patients are treated and that they receive the right prophylaxis. Ongoing clinical research and evidence-based medicine reviews suggest that blanket approaches that give the same medication to all patients without risk stratification may not be beneficial and may even cause more harm than benefit.[9-11]

New Medications for VTE prophylaxis

New versions of low molecular weight heparins (LMWH) are being brought to market, with additional newly approved indications by the U.S. Food and Drug Administration (FDA). In addition, other medications with different pathways of action are being researched and approved. Most recently in July 2011, rivaroxiban, an oral direct Factor Xa inhibitor, was approved by the FDA for prophylaxis of DVT/PE in adults undergoing hip and knee replacement surgery. Dabigitran, an oral direct thrombin inhibitor, is FDA approved for prevention of stroke in patients with non-valvular atrial fibrillation. Although it is not currently approved for VTE prophylaxis in the United States, it is being used in this capacity in some European countries and Canada. A recent systematic review and meta-analysis of three novel oral agents, dabigatran, apixaban and rivaroxaban, for VTE prophylaxis after total hip and total knee replacement surgery found no difference in net clinical benefit. In fact, this review reported that success in prevention of VTE was inversely associated with clinically relevant bleeding.[12] These findings are indicative of the diminishing returns associated existing medications developed to prevent VTE and highlight the need to improve prescription of the best-practice medications currently available.[13]

Inferior Vena Cava Filters

New technologic advances in devices to prevent DVT from becoming PE via mechanically trapping the clot in the inferior vena cava before they can reach the heart and lungs may be beneficial in some patient populations. Although originally designed for permanent use, multiple approved devices can now be placed for temporary (also known as “optional” or “retrievable”) prophylaxis and then removed at a later date. However, the evidence to support the use of this technology is unclear.

For example, the placement of inferior vena cava filers (IVCFs) is rapidly increasing among trauma patients[14] for primary prophylaxis against PE even in patients without proven DVT. Clinical uncertainty remains about whether prophylactic IVCFs should be used in trauma. Current guidelines from the American College of Chest Physicians (ACCP)[1] and the Eastern Association for the Surgery of Trauma (EAST)[15] have diametrically opposed opinions on the use of IVCFs for primary PE prophylaxis. An ongoing AHRQ sponsored Evidence-based Practice Center Systematic Review Protocol entitled “Comparative Effectiveness of Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism among Special Populations” will assess the role of IVCFs in the prevention of pulmonary embolism in trauma and other special populations (including those patients undergoing bariatric surgery).

What Approaches Have Been Used To Improve Appropriate VTE Prophylaxis?

Evolution of information technology is enabling development of more sophisticated clinical decision support systems to improve compliance with guidelines. Several recent examples are described below.

Lesselroth et al,[16] developed a clinical decision support-enabled order menu in their computerized patient record system (CPRS) to recommend appropriate VTE prophylaxis at the time medication orders are written at the Portland Oregon VA Medical Center. After identifying and addressing some key initial limitations (providers could unintentionally or intentionally bypass the order menu and recommended guidelines), use of the order menu increased from 20 percent to 80 percent. This study underscores the need for interventions to integrate well into provider workflow and ideally be mandatory without any possibility of ignoring or bypassing the VTE algorithm. Alerts and systems are only effective if they consistently reach their intended target.

In the study by Beeler et al,[17] an electronic alert was displayed in the medical chart of every hospitalized medical patient who did not have pharmacological or mechanical VTE prophylaxis ordered within 6 hours after admission and had documented VTE risk. Rates of thromboprophylaxis orders among medical patients significantly increased from pre-implementation rates of 43.4 percent to 66.7 percent ($p<0.0001$) during the 4 months after implementation. The following year, thromboprophylaxis orders increased further to 73.6 percent ($p=0.011$).

Kucher et al,[18] proactively searched for hospitalized patients at risk for developing VTE who were not prescribed prophylaxis (pharmacological or mechanical). Electronic alerts were sent to providers of patients randomized to the intervention group that their patient was at risk for VTE. Patients in the intervention group were significantly more likely to receive mechanical prophylaxis ($p<0.001$) and significantly more likely to receive prophylactic doses of unfractionated heparin ($p<0.001$). There were no significant changes to orders of enoxaparin ($p=0.18$) or warfarin ($p=0.11$) between intervention and control groups. In addition, patients in the intervention group were significantly more likely to be free from DVT or PE after 90 days ($p<0.001$). This approach is reactive – it identifies patients who were not initially ordered prophylaxis and then attempts to correct the patient safety problem, rather than suggesting and improving rates of prophylaxis at the appropriate time of initial treatment.

In 2008, a mandatory, computerized decision support-enabled VTE risk stratification order set was implemented in the computerized provider order entry system at the Johns Hopkins Hospital to recommend ACCP guideline-appropriate, service-specific (e.g. medicine, general surgery, trauma, etc.) prophylaxis for an individual patient's risk stratum.[19,20] Within the first year, adherence to guideline-appropriate VTE prophylaxis increased significantly hospital-wide and rates of VTE have been on a decreasing trend. This system overcomes the downsides of the Kucher approach since it requires proactive risk stratification during the completion of the admission order set for all admitted patients and therefore is nearly 100 percent effective at forcing providers to assign an appropriate risk stratum to all patients within 24 hours of hospital arrival.[21] However, this system remains fallible since the guideline-suggested VTE prophylaxis is merely a recommendation; it is not mandatory and may be ignored.

What Have We Learned About These Practices?

What Are the Beneficial Effects of VTE Prophylaxis?

The original "Making Health Care Safer" report focused on the evidence for effectiveness of specific clinical interventions (i.e. medications and mechanical prophylaxis) for specific clinical situations, and concluded that there was extensive evidence supporting their effectiveness and low cost, particularly after certain types of surgical procedures, trauma, and medical conditions such as cerebrovascular accidents.[22] Quality improvement-related interventions such as practice guidelines, clinical decision support systems, and educational interventions to change provider behavior were addressed in separate chapters in the original support. A few studies found beneficial effects of clinical decision support systems and educational interventions, both separately and combined.

The updated evidence for VTE prophylaxis in selected patients has been well-described in a variety of recent evidence-based clinical guidelines and systematic reviews.[1,10,15] The evidence for clinical interventions for VTE prophylaxis remains strong in specified populations, and prophylaxis is recommended by practice guidelines for those patients, although it should not be applied universally. Since the availability of medications and condition-specific evidence is rapidly evolving and these guidelines are regularly updated, this evidence is not summarized here, and the remainder of this section focuses on interventions intended to improve compliance with risk-appropriate VTE prophylaxis among different patient populations.

Interventions to Improve Prophylaxis Adherence

A systematic review of interventions to improve VTE prophylaxis use in hospitals, based on literature searches from 1996-2003, found 30 eligible studies; only one was an RCT and only three had concurrent controls. Strategies included passive dissemination, which had little effect (50% compliance), single-strategy studies (12 studies—audit and feedback, documentation aids, and quality assurance activities all produced about 80% compliance), and clinical decision support systems approached 100 percent compliance. Twelve studies incorporated two or more strategies, usually including an educational component, and all demonstrated improvements in use of VTE prophylaxis. In addition to the types of strategies used in the single-strategy studies, these studies also included strategies such as advertising, appointment of specific implementation staff, and recruitment of local change agents or opinion leaders. Most studies evaluated change in provider behavior, not patient outcomes, and no study that evaluated outcomes demonstrated a reduction in DVT or PE rates, often due to lack of adequate power.[23]

Interventions to improve adherence to prophylaxis include implementation of clinical decision support tools, financial disincentives, and outcomes reporting. Clinical decision support tools have the potential to improve adherence to guideline-appropriate prophylaxis ordering[24,25] which may then have a sustained impact on clinical outcomes. While this method has classically taken the form of paper-based order-sets, as computerized provider order entry systems are adopted in hospitals across the country, an opportunity exists to build electronic clinical decision support into these systems to evaluate, risk stratify patients based on individual patient risk factors and recommend the appropriate VTE prophylaxis strategies.

Outcomes reporting is another approach to improve VTE prophylaxis, through feedback and public reporting or the financial incentive of nonpayment for VTE events. The Centers of Medicare and Medicaid Services (CMS) placed VTE after orthopedic hip/knee replacement on their list of "never events" for which providers will not be reimbursed. However, even with best

practice, not all VTE events can be prevented;[26,27] it has been estimated that best practice prophylaxis may reduce incidence of DVT by up to 70 percent.[1] Another potential limitation to the use of DVT/PE rates alone to measure quality is the significant issue of surveillance bias—because many DVTs are clinically silent and therefore go undetected without routine screening.[28] For example, in the field of trauma surgery, clinical ambiguity persists regarding the clinical and cost effectiveness of the screening of high-risk asymptomatic trauma patients for DVT with duplex ultrasound.[28] As a result, certain providers and hospitals report higher DVT rates due entirely to higher rates of diagnostic testing- a classic example of surveillance bias.[29-31]

Because of these issues—and variation in patient risk—unadjusted VTE rates are likely not appropriate for public reporting. A better definition of preventable harm may be obtained by combining an outcome and process measure rather than relying on an outcome alone. For example, it has been suggested that only VTE events occurring in patients who did not receive adequate prophylaxis should be labeled a "preventable VTE."[28] This approach and specific definition has been incorporated as one of the six Meaningful Use Quality Measures related to VTE,[22] although this measure has not yet been evaluated for its impact on VTE prophylaxis compliance.

Conclusions and Comment

Strong evidence from numerous high-quality trials supports the effectiveness of VTE prophylaxis for specific populations, although there are significant risks and risk stratification is necessary to ensure that prophylaxis is targeted to appropriate patients. However, rates of VTE prophylaxis are suboptimal, and VTE remains a difficult and elusive crisis in patient safety. Less evidence exists on which interventions are effective for increasing rates of VTE prophylaxis in appropriate populations. As with other patient safety interventions, educating providers on the benefits of appropriate VTE prophylaxis alone is not an effective strategy to improve appropriate use of VTE prophylaxis. Evidence, although mostly low-quality, non-randomized studies without concurrent controls, supports that education combined with other quality improvement strategies, and information technology approaches such as mandatory computerized clinical decision support, appear to offer the most effective approaches to promote best practice prophylaxis use and prevent patient harm resulting from VTE. A summary table is located below (Table 1).

Table 1, Chapter 28. Summary table

Scope of the Problem Targeted by the PSP (Frequency/Severity)	Strength of Evidence for Effectiveness of the PSPs	Evidence or Potential for Harmful Unintended Consequences	Estimate of Cost	Implementation Issues: How Much do We Know?/How Hard Is it?
Common/Moderate	High	Moderate (bleeding)	Low	Little/Moderate

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